Lauren A. Quinn[1], Sunaya H. Hirani[2], Thomas C. Williams[3,4,6], Ian P. Sinha[2,5,6]

iansinha@liverpool.ac.uk

@wheezylikesund1; @williams_t_c

Viewpoint

Palivizumab immunoprophylaxis for infants with BPD has medium- and long-term benefits: myth or maxim?

Cite as: Quinn LA, Hirani SH, Williams TC, *et al*. Palivizumab immunoprophylaxis for infants with BPD has medium- and long-term benefits: myth or maxim? *Breathe* 2021; 17: 210110.

Early life experiences determine respiratory health through the life course. A complex interplay of antenatal and early years adverse exposures are implicated in the development of childhood asthma. COPD is, in around half of the people with the condition, a manifestation of suboptimal airway development in infancy and childhood [1, 2]. In this article, we discuss medium- and long-term effects at the intersection between two early life problems: respiratory syncytial virus (RSV) bronchiolitis and the lung sequelae of prematurity, specifically bronchopulmonary dysplasia (BPD). We focus on whether immunoprophylaxis against RSV in infants with BPD confers medium- and long-term benefits.

Respiratory consequences of preterm birth

Around one in 10 infants is born prematurely (before 37 weeks gestational age). There is a direct relationship between gestation at birth and risk of lung sequelae, reflecting both the degree of lung immaturity and complications of neonatal intensive care, including ventilator-induced lung injury, oxygen toxicity, upper airway mechanical damage, and abnormal microbiological colonisation and infection. These factors lead to abnormal alveolarisation, changes in the extracellular matrix of the lung parenchyma, and maldevelopment of pulmonary vasculature. This lung damage, together with an increased risk of an immature central respiratory drive, may lead to an oxygen requirement beyond 36 weeks gestational age (BPD). Preterm infants with BPD (when compared with preterm infants without BPD and full-term infants) have an increased risk of hospitalisation in the first 2 years of life, higher likelihood of wheeze and other breathing disorders in childhood, and lung function abnormalities that persist through the life course [3]. Management of BPD involves a focus on nutrition, using home oxygen to prevent hypoxia and pulmonary hypertension, and minimising the risk of other problems, such as infection, in order to optimise lung growth in infancy and early childhood [4].

Babies with BPD are given palivizumab to prevent severe bronchiolitis

RSV is a negative sense, single-stranded RNA virus that commonly causes respiratory infections in all age groups. By the age of 1 year it is estimated that 69% to 98% of infants will have been infected [5, 6]. Those most at risk from severe infection and death are infants [7], as are individuals with cardiac, respiratory and other comorbidities [8]. RSV is now the leading cause of hospitalisation

@ERSpublications
It is uncertain whether immunoprophylaxis against RSV protects preterm babies with BPD against future respiratory problems. It is biologically plausible that it does, at least in some infants.
https://bit.ly/3ikzwZD

in infants and children due to bronchiolitis and pneumonia globally [9], with an estimated 33.1 (uncertainty range 21.6–50.3) million cases, 3.2 (2.7–3.8) million hospitalisations, and 118000 (94600–149400) deaths in children under 5 years of age in 2015, with the bulk of these concentrated in low- and middle-income countries (LMICs) [7]. In high-income settings, RSV bronchiolitis is the single largest cause of admission in infants, constituting an estimated 18% of all hospital admissions in those aged under 1 year, and 12% of paediatric intensive care unit admissions for those aged under 5 years [10]. As well as the direct burden of infection (estimated at USD 6 billion in 2017) [11], RSV has a significant indirect burden. In high income settings, a single episode of hospitalised RSV infection in an infant is estimated to lead to a loss of 7 days of economic activity amongst caregivers [12].

Prematurity increases the risk of serious infection with RSV bronchiolitis. Preterm infants, especially those with BPD, are up to four times more likely to require hospitalisation for bronchiolitis than those born at term [13, 14]. There are various reasons for this: smaller lung volumes, narrower airways, and hypoalveolarisation render them at risk because of reduced respiratory reserve in the face of infection [15]. The virological actions of RSV, that drive inflammation, pulmonary oedema and epithelial sloughing, cause an additional hit to lungs that are already vulnerable. Another important factor is immune system immaturity. The lack of antenatal maternal antibody transfer, due to preterm birth, causes impaired protection against RSV.

Palivizumab is a humanised monoclonal antibody (mAb) administered to high-risk infants to reduce the risk of hospitalisation from RSV bronchiolitis. It works by binding to the F (fusion) glycoprotein of RSV and preventing entry of the virus into epithelial cells. It is administered monthly, by injection, during the RSV season. Randomised controlled trials (RCTs) have demonstrated a relative reduction in the risk of hospitalisation from RSV bronchiolitis ranging from 39% to 82% [16, 17]. As with other mAbs, palivizumab is expensive and is largely used in high-income settings.

Does RSV bronchiolitis increase the risk of respiratory illness through the life course?

Bronchiolitis can disrupt various components of the respiratory system associated with the development of asthma [18]. These include inflammation causing imbalance of T-helper cell differentiation, disruption of normal respiratory microbiota, and abnormal effects on neurogenic airway control. In addition, there may be iatrogenic factors that increase the risk of subsequent asthma. Certain infants who develop severe bronchiolitis may require high levels of respiratory support that can damage airways, and some may be treated for presumed secondary bacterial infection, which is relevant given recent evidence that antibiotic use in infancy may be associated with later asthma.

A recent meta-analysis included 32 observational studies (including nearly 300000 infants) examining the association between bronchiolitis in the first 2 years of life, and development of asthma in childhood [19]. The pooled results demonstrated that infants who developed bronchiolitis before 2 years of age were more than twice as likely to develop asthma or wheezing at some point in childhood (relative risk (RR) 2.46, 95% CI 2.14–2.82, $p<0.001$). The pooled results of 15 studies (82000 infants) included in a previous meta-analysis specifically focussed on whether hospitalisation with RSV-positive bronchiolitis was associated with an increased risk of asthma or wheezing [20]. Infants hospitalised for RSV had a significantly increased risk of wheeze/asthma in childhood (odds ratio (OR) 3.84, 95% CI 3.23–4.58). It is unclear how many of these studies included preterm infants, or those with BPD, so it is not possible to say whether they are at particular risk of medium- and long-term sequelae from RSV bronchiolitis. One systematic review examined whether RSV bronchiolitis led to changes in pulmonary function [21]. The results were inconsistent. Across 29 studies, 16 found an association between RSV bronchiolitis in infancy and lung function abnormalities (typically airway obstruction) in later childhood. There are difficulties in interpreting the evidence in these three systematic reviews as there is heterogeneity between studies in the populations and settings, the definitions of bronchiolitis and asthma, and the timepoints at which infants are followed-up.

A key issue with these large-scale observational studies is understanding whether there is a true causal link between the exposure (bronchiolitis) and the outcome (asthma, abnormal lung function), or one mediated by confounding variables. For example, impaired lung function at birth might predispose infants to both bronchiolitis and later asthma. A recent systematic review aimed to evaluate the possibility of a causal relationship between RSV and subsequent wheezing illness [22]. Importantly, when genetic predisposition for asthma was accounted for in studies the magnitude of the association between RSV and subsequent wheezing was markedly attenuated.

No studies have directly examined whether RSV bronchiolitis in infancy leads to an increased risk of adult respiratory disease. However, results of long-term cohort studies show associations between childhood infection and wheezy episodes

and a "persistently low lung function" trajectory through adult life [1, 2], and between "asthma-like symptoms" in early childhood and the development of COPD in later life [23].

Does palivizumab reduce the risk of respiratory illness in childhood and adulthood?

Two recent systematic reviews have examined whether RSV prophylaxis can reduce the risk of wheezing in childhood. One, by our group [24], included eight studies (two of which were RCTs) of 11195 infants. A pooled analysis across these studies demonstrated that a reduction in the relative risk of developing recurrent wheeze or asthma was not statistically significant (RR 0.60, 95% CI 0.31–1.16). *A priori* subgroup analyses that excluded studies of very low quality, and which examined late preterm infants, did demonstrate statistically significant results (RR 0.42 (95% CI 0.22–0.80, p=0.008) and RR 0.35 (95% CI 0.14–0.86, p=0.02), respectively). The primary analysis of another review also found no statistically significant difference in the risk of wheezing illness amongst infants who had not received RSV prophylaxis (OR 1.21, 95% CI 0.73–1.99) [22]. This large confidence interval reduces the extent to which one can be certain about the results of the studies. These reviews identified one RCT examining whether palivizumab reduced wheezing illnesses in preterm infants, but notably the study excluded those infants with BPD [25], and one RCT evaluated another MAb, Motavizumab [26], in healthy Native American infants.

Summary and future directions

It is plausible that in some infants with BPD, RSV bronchiolitis may increase the risk of subsequent wheezing and asthma. This has, however, not been evaluated in observational longitudinal studies. It is also plausible that if infants with BPD develop RSV bronchiolitis, they may be at increased risk of COPD in later life as a consequence of impaired lung development. Again, this has not yet been studied. On current evidence, there is little to suggest that when given to all babies with BPD palivizumab reduces the risk of childhood asthma or wheeze. There have been no studies, to our knowledge, that evaluate palivizumab's impact on subsequent lung function. As other mAbs (such as nirsevimab, a long acting monoclonal) and preventative strategies for RSV (such as maternal immunisation) are evaluated in trials, and are brought to market, research to evaluate their medium- and long-term benefits would be of interest.

Notwithstanding this current lack of evidence, it is important that we consider longer term outcomes in infants with BPD. Preventing infection is likely, at least in some babies, to protect their airways from further damage that may manifest in childhood or adulthood as significant problems. However, we do not know who those babies are on the basis of current evidence. What we do know, however, is that socioeconomic and environmental factors are a major factors in determining the risk of preterm birth and lung development more generally. Strategies to address these problems must be factored into preventative models of healthcare, to give infants with BPD the best chance to outgrow their respiratory impairment.

Affiliations

Lauren A. Quinn[1], Sunaya H. Hirani[2], Thomas C. Williams[3,4,6], Ian P. Sinha[2,5,6]

[1]Queens University Belfast School of Medicine Dentistry and Biomedical Sciences, Belfast, UK. [2]Alder Hey Children's NHS Foundation Trust, Liverpool, UK. [3]Dept of Paediatric Respiratory and Sleep Medicine, Royal Hospital for Children and Young People, Edinburgh, UK. [4]Department of Child Life and Health, University of Edinburgh, Edinburgh, UK. [5]Division of Child Health, University of Liverpool, Liverpool, UK. [6]Joint senior authors.

Conflict of interest

I.P Sinha, S.H. Hirani, and L.A. Quinn have no interests to declare. T.C. Williams sits on the Laboratory Technical Committee for Phase 2 of the WHO Global RSV Surveillance Programme.

References

1. Bui DS, Lodge CJ, Burgess JA, *et al.* Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018; 6: 535–544.
2. Belgrave DCM, Granell R, Turner SW, *et al.* Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *Lancet Respir Med* 2018; 6: 526–534.
3. Dassios T, Greenough A. Long-term sequelae of bronchopulmonary dysplasia. *In:* Sinha IP, Bhatt JM, Cleator A, *et al.*, eds. Respiratory Diseases of the Newborn Infant. Sheffield, European Respiratory Society, 2021; 68–78.

4. Rose K, Woodland C, Murphy G, *et al.* Management of bronchopulmonary dysplasia: strategies to prevent short- and long-term complications following discharge from the NICU. *In:* Sinha IP, Bhatt JM, Cleator A, *et al.*, eds. Respiratory Diseases of the Newborn Infant. Sheffield, European Respiratory Society, 2021; 79–88.
5. Glezen WP. Risk of primary infection and reinfection with respiratory syncytial virus. *Arch Pediatr Adolesc Med* 1986; 140: 543.
6. Henderson FW, Collier AM, Clyde WA, *et al.* Respiratorysyncytialvirus infections, reinfections and immunity. A prospective, longitudinal study in young children. *N Engl J Med* 1979; 300: 530–534.
7. Shi T, McAllister DA, O'Brien KL, *et al.* Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet* 2017; 390: 946–958.
8. Bont L, Checchia PA, Fauroux B, *et al.* Defining the epidemiology and burden of severe respiratory syncytial virus infection among infants and children in western countries. *Infect Dis Ther* 2016; 5: 271–298.
9. O'Brien KL, Baggett HC, Brooks WA, *et al.* Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *Lancet* 2019; 394: 757–779.
10. Green CA, Yeates D, Goldacre A, *et al.* Admission to hospital for bronchiolitis in England: trends over five decades, geographical variation and association with perinatal characteristics and subsequent asthma. *Arch Dis Child* 2016; 101: 140–146.
11. Zhang S, Akmar LZ, Bailey F, *et al.* Cost of respiratory syncytial virus-associated acute lower respiratory infection management in young children at the regional and global level: a systematic review and meta-analysis. *J Infect Dis* 2020; 222: S680–S687.
12. Mitchell I, Defoy I, Grubb E. Burden of respiratory syncytial virus hospitalizations in Canada. *Can Respir J* 2017; 2017: 4521302.
13. Gouyon J-B, Rozé J-C, Guillermet-Fromentin C, *et al.* Hospitalizations for respiratory syncytial virus bronchiolitis in preterm infants at <33 weeks gestation without bronchopulmonary dysplasia: the CASTOR study. *Epidemiol Infect* 2013; 141: 816–826.
14. Fauroux B, Gouyon J-B, Roze J-C, *et al.* Respiratory morbidity of preterm infants of less than 33 weeks gestation without bronchopulmonary dysplasia: a 12-month follow-up of the CASTOR study cohort. *Epidemiol Infect* 2014; 142: 1362–1374.
15. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. *Pediatrics* 1988; 82: 199–203.
16. Bonadies L, Priante E, Baraldi E. Prophylaxis against respiratory syncytial virus in high-risk infants. *In:* Sinha IP, Bhatt JM, Cleator A, *et al.*, eds. Respiratory Diseases of the Newborn Infant. Sheffield, European Respiratory Society, 2021; 361–371.
17. Rodriguez-Fernandez R, Mejias A, Ramilo O. Monoclonal antibodies for prevention of respiratory syncytial virus infection. *Pediatr Infect Dis J* 2021; 40: S35–S39.
18. Midulla F, Nenna R. Bronchiolitis in infants and wheeze in preschool children. *Breathe* 2011; 8: 32–37.
19. Wang G, Han D, Jiang Z, *et al.* Association between early bronchiolitis and the development of childhood asthma: a meta-analysis. *BMJ Open* 2021; 11: e043956.
20. Régnier SA, Huels J. Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: systematic review and meta-analysis. *Pediatr Infect Dis J* 2013; 32: 820–826.
22. Brunwasser SM, Snyder BM, Driscoll AJ, *et al.* Assessing the strength of evidence for a causal effect of respiratory syncytial virus lower respiratory tract infections on subsequent wheezing illness: a systematic review and meta-analysis. *Lancet Respir Med* 2020; 8: 795–806.
23. Bisgaard H, Nørgaard S, Sevelsted A, *et al.* Asthma-like symptoms in young children increase the risk of COPD. *J Allergy Clin Immunol* 2021; 147: 569–576.
24. Quinn L, Shields MD, Sinha I, *et al.* Respiratory syncytial virus prophylaxis for prevention of recurrent childhood wheeze and asthma: a systematic review. *Syst Rev* 2020; 9: 269.
25. Blanken MO, Rovers MM, Molenaar JM, *et al.* Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants. *N Engl J Med* 2013; 368: 1791–1799.
26. O'Brien KL, Chandran A, Weatherholtz R, *et al.* Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. *Lancet Infect Dis* 2015; 15: 1398–1408.